REMARKS

Claims 1-6, 10-13, 23, 28-30, 40-42 and 75-83 are pending in the instant application. Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn without prejudice for being directed to a non-elected invention. Claims 6, 10-13 and 77-83 stand rejected. Claim 6 is amended herein. Support for the definition of mutation level can be found, for example, in the legend of Figure 8 on page 14, line 26 to page 15, line 2; and support for the amendment for quantifying the reaction product is provided, for example, on page 19, lines 2-3, page 55, lines 13-15, page 62. line 7, and page 79, lines 15-20. Claim 10 is cancelled without prejudice. Claims 84 to 86 have been added. The claims are supported, for example in Figure 12 and its legend on page 15, lines 21-30. No new matter is added by the amendments.

Claim Objections

Claim 10 has been objected to for being redundant to claim 6. Claim 10 has been cancelled.

Claim 6 has been objected to for containing minor grammatical errors. Applicant thanks the Examiner for careful reading of the claims. Claim 6 has been amended as requested.

Rejection under 35 U.S.C. §112, First Paragraph for Lack of Enablement

The Office Action has rejected claims 6, 10-13, and 77-83 for not being enabled by the specification. Specifically the Office Action asserts that the specification is not enabling for the scope of organisms claimed. Without agreeing with the rejection, Applicant has amended the claims to recite that the subject is a human subject. Withdrawal of the rejection is respectfully requested.

Rejection of Claims under 35 U.S.C. §103

The Office Action has maintained the rejection of claims 6, 10-13, and 77-81 for allegedly being unpatentable over Schouten et al (2002) in view of Maire et al. (2002) and Lecomte (2002).

The Office Action has further rejected claims 82 and 83 for allegedly being unpatentable over Schouten et al (2002) in view of Maire et al. (2002), Lecomte (2002) and Nazarenko.

For the sake of brevity, the rejections will be addressed simultaneously. The rejection fails because there is no suggestion to combine the teachings of Marie and Schouten for at least the following reasons.

The Office Action asserts that Schouten teaches the detection method instantly claimed. Applicant respectfully disagrees that the method provided by Schouten is the same as the method that is claimed. However, as the Office Action notes, Schouten provides no teachings in regard to analysis of a G35A KRAS mutation. The salient feature distinguishing this from Schouten is **conversion**. A relatively subtle human mutation is converted into a segment of foreign DNA, thus allowing easy detection and quantification. This conversion step is noted, for example, on page 89, line 2.

This deficiency of the teachings of Schouten are alleged to be overcome by Marie. The Office Action asserts that the mutation analyzed by the allele specific amplification is taught by Marie. The Office Action states that "With regard to the limitations of claims 11 and 12, the teachings of Marie et al indicate that a mutation level of 0.0% (e.g., undetected KRAS mutation) is indicative of chronic pancreatitis (claim 11), and a mutation level of 100% (e.g., KRAS mutation detected in all samples from a subject) is indicative of pancreatic cancer" (see page 9). Further, the Office Action states that the term "mutation levels" is read with the broadest reasonable interpretation.

Applicant has amended claim 6 as set forth above to provide the definition of "mutation level" as provided in the paragraph bridging pages 14 and 15. The claim has further been amended to recite that the mutation level is a mutation level for a single sample, not a mutation level for a population. Applicant submits that the amendment does not alter the scope of the claim as it simply imports a definition present in the specification.

The claim has been further amended to recite that the amount of reaction product is quantified. There can be no teaching or suggestion from Marie to quantify the amount of reaction product in a single sample as claimed, rather than in a population.

Applicant submits that Marie does not teach a mutation level of 100% being indicative of pancreatic cancer and a mutation level of 0% being pancreatitis. In fact, Marie does not teach or suggest analysis of a mutation level. Marie performs an assay to detect **only** mutated KRAS in a sample as shown in the paragraph bridging the two columns on page 552. As no detection of normal KRAS is performed, not mutation level can be determined. Detection for Marie is purely binary. There is no suggestion that the amount of the mutation present would be diagnostic.

Further, Marie teaches that only 44% of those with cancer were found to have a KRAS mutation. Therefore, Marie teaches that over half the time the test is wrong. Cancer is not detected because **a mutation level of 0% is detected by Marie despite the presence of cancer**. Conversely, 13% of those with chronic pancreatitis were found to have a KRAS mutation. That is **a mutation level of 100% is detected by Marie despite the absence of cancer**. Per the suggestion of the Office Action, 13% of those with chronic pancreatitis would have a mutation level of 100% and therefore have cancer.

Having determined that subjects having chronic pancreatitis, and not having cancer, have KRAS mutations, Marie searched for another method to categorize subjects as having pancreatic cancer or not having pancreatic cancer. Marie determined that **the method should not be nucleic acid based** due to the presence of KRAS mutations in samples from subjects who did not have cancer. It was obvious to Marie, and would be obvious to one of skill in the art, that a more sensitive method to detect mutations in samples would not provide a better method of detection. **One of skill in the art might even expect that the use of a more sensitive assay, such as that provided by Schouten, would result in the detection of more false positives in samples from subjects having chronic pancreatitis.** It was clear to Marie that a

completely different type of assay should be combined with the PCR based assay to differentiate between subjects having pancreatic cancer and subjects having chronic pancreatitis.

Section 2144 sets forth potential rationales for combining references.

> >II. < THE EXPECTATION OF SOME ADVANTAGE IS THE STRONGEST RATIONALE FOR COMBINING REFERENCES
>
> The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, **that some advantage or expected beneficial result would have been produced by their combination**. *In re Sernaker,* 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). >See also *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick*, 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) (emphasis added).

As the samples themselves cause the false positives, no advantage or expected beneficial result would have been produced by the combination of Maire with a reference that teaches a detection method in which lower levels of KRAS can be detected.

There can be no advantage expected by the combination of Marie and Schouten. There can be no motivation to combine the teachings of Marie and Schoten. In fact, as noted above, one of skill in the art could easily see a disadvantage in combining the methods of Marie and Schouten. The fact that two references can be combined does not mean that there is motivation to combine the references. Applicant respectfully requests that a reason be provided that one of skill in the art would be motivated to modify Marie to provide a more sensitive nucleic acid based assay for the detection of KRAS mutations when KRAS mutations provide so many false positives.

The Office Action notes that "a method comprising **KRAS analysis with serum CA 19.9 levels** allows for 98% sensitivity." As noted in the Office Action, the method of Marie requires both detection of the presence or absence of KRAS muations and CA 19.9 levels. That is **Marie requires two distinct tests, one nucleic acid based and one not nucleic acid based,** to provide a satisfactory test. In the last paragraph, Marie

states "In conclusion, although detection of plasma *KRAS2* mutations in circulating DNA is not a definitive argument for malignancy, **it could contribute to cancer diagnosis**." That is, the *KRAS2* and CA 19.9 assays should be used in conjunction with each other, or at least the KRAS2 assay should not be used alone. As stated in Section 2144.04(II) of the MPEP:

> B. Omission of an Element with Retention of the Element's Function Is an Indicia of Unobviousness
>
> **Note that the omission of an element and retention of its function is an indicia of unobviousness**. *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966) (Claims at issue were directed to a printed sheet having a thin layer of erasable metal bonded directly to the sheet wherein said thin layer obscured the original print until removal by erasure. The prior art disclosed a similar printed sheet which further comprised an intermediate transparent and erasure-proof protecting layer which prevented erasure of the printing when the top layer was erased. The claims were found unobvious over the prior art because the although the transparent layer of the prior art was eliminated, the function of the transparent layer was retained since appellant's metal layer could be erased without erasing the printed indicia.). (emphasis added)

The instant invention allows for omission of an element, that is omission of the test for CA 19.9 levels, and reliance on a nucleic acid based test only, while providing a test that is useful for distinguishing between subjects having pancreatic cancer and subjects having chronic pancreatitis. However, Applicant notes that the method does not preclude the use of additional tests for the purpose of diagnosis. The assertion in the Office Action that the claims recite a method "comprising" the diagnostic assay claimed, and could be combined with a test to detect CA 19.9 levels is not relevant to the obviousness rejection. An obviousness rejection must consider if the instantly claimed invention would have been obvious to one of skill in the art at the time of filing of the instant application. That is what would have been obvious to one of skill in the art prior to the filing of the instant application. **A particular combination of references or modification of a reference is or is not proper independent of the claims being examined**. The combination of Schouten and Marie cannot be proper. Modification of Marie to rely on only a nucleic acid based test cannot be proper. Moreover, the

combination of Marie and Schouten does not provide the instantly claimed invention for the reasons discussed above.

Applicant submits that one of skill in the art at the time of filing the instant application would not be motivated to modify Marie to exclude the test for CA 19.9 levels in view of the low sensitivity and specificity of the nucleic acid based test. The false positives, i.e., **the detection of KRAS in samples from subjects not having pancreatic cancer is not a problem with the detection method itself**. On page 553, second full paragraph, Marie notes that *KRAS2* mutations have been reported in pancreatic tissue or juice of 6-42% of patients with chronic pancreatitis. In the second full paragraph of the reference, Marie teaches that *KRAS2* mutations had been found in 75-95% of pancreatic cancers and 63-83% of samples from pure pancreatic juice. All of these studies cited by Marie demonstrate that one of skill in the art analyzed samples for the presence or absence of a *KRAS2* mutation, and that detection of the presence or absence of *KRAS2* mutations would not likely provide sufficient information to distinguish between pancreatic cancer and chronic pancreatitis.

In the abstract, Marie states:

> Detection of *KRAS2* mutations in circulating deoxyribonucleic acid has a low sensitivity but a specificity of about 90% for the diagnosis of pancreatic cancer. It seems particularly useful when serum carbohydrate antigen 19.9 levels are normal or inconclusive. A **combined** normal serum carbohydrate antigen 19.9 and absence of circulating *KRAS2* mutation makes the diagnosis of pancreatic cancer extremely unlikely. (emphasis added)

In other words **Marie states looking at the presence or absence of mutations in *KRAS2* is not sufficient to differentiate between cancer and chronic pancreatitis**. A completely different marker must be used to provide a reliable assay. One of skill in the art would not be motivated to modify Marie to not include the CA 19.9 assay in combination with the *KRAS2* assay.

Neither Lecomte nor Nazarenko compensate for the deficiencies in the motivation to combine Schouten and Marie. Withdrawal of the rejection is respectfully requested.

New Claims

Applicant has added new claims 84-86 to recite the mutation level that can be detected by the method. This sensitivity is far greater than that achieved by Schouten. The quantification provided by Schouten does not teach or suggest the sensitivity demonstrated in the instant application. For example, on page 8 of 13, first column, Schouten et al. teaches that

> The excellent reproducibility of relative signals obtained enabled the detection of a single extra copy of a probe target sequence per diploid genome.

That is, a 50% increase in copy number could (surprisingly) be detected.

The method of Schoten designed predominantly to detect large deletions (1N) or additions (3N) in genomic DNA, where the normal copy number is 2N. It can be used to detect 3 copies of chromosome 21 (Down's syndrome) or the X chromosome, whole exon deletions of BRCA2, exon losses of the mismatch repair gene hMLH1 and hMSH2, loss of the tumor suppressor gene p16/cdkn2b, extra copies (amplification) of erbb2, and germline mutation of the cystic fibrosis gene, cftr.

Detection in gains and losses in chromosomal regions refer to increases of 1.5-6.5 fold (page 9 of 13, second column-page 10 of 13, first column). A point mutation is detected in a heterozygote carrying a CFTR mutation that causes cystic fibrosis. The results from the assay are shown in Figure 8. The inequality in the size of the wild-type and F508 mutant peaks, when the sequences would be expected to be present in identical amounts, would suggest to one of skill in the art a limit on the accuracy of the determination of relative quantities of nucleic acid sequences.

In the Discussion section, possible applications are considered by Schouten (see page 12 of 13, second column). All of the applications consider fold changes in the amount of a particular sequence present. Based on the teachings of Schouten et al., one could not expect the claimed cut-offs could be useful or even detected using the method provided therein.

In view of the foregoing amendments and remarks, Applicant submits that the instantly claimed invention would not have been obvious over Schouten in view of Marie. Withdrawal of the rejection is respectfully requested.

CONCLUSIONS

In view of the above amendments and remarks, Applicants believe the pending application is in condition for immediate allowance. However, if the Examiner believes that there are any outstanding issues in the case that could be addressed by telephone conference, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss the matter.

PETITION AND FEE AUTHORIZATION

It is believed that there is no fee due with this response. However, if a fee is due, the Commissioner is authorized to charge any fees associated with this submission, or any other submission by this Firm in relation to the instant application, to our Deposit Account, No. 04-1105, Reference 62310(71699). Any overpayment should be credited to said Deposit Account.

Dated: March 24, 2010

Respectfully submitted,

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